

wherein the R¹R²CH group in the 5-position of the cyclic parent structure and the hydroxy group in the 3-position of the cyclic parent structure are each in the trans position relative to each other and wherein the substituent R⁴ in the 4-position and the hydroxy group in the 3-position of the cyclic parent structure are each in the cis position relative to each other, and wherein

n is 0 or 1,

R¹ is hydrogen;

R² is hydrogen;

R³ is hydrogen, and

R⁴ is hydrogen or lower alkyl, or

R³ and R⁴ also together are a C₃-C₆-

alkylene chain optionally containing 1 to 3 double bonds or together form the 7, 7-dimethylbicyclo[3.1.1] heptyl-system

R⁵ is hydrogen or lower alkyl, and

R⁶ is hydrogen, and

R⁷ is hydrogen, and

R⁸ is hydrogen;

a monocyclic or bicyclic ring system selected from the group consisting of cyclopropyl, cyclopentyl cyclohexyl, phenyl, p-bromophenyl and 3-indolyl;

lower alkyl, phenyl-lower alkyl or lower-alkoxy lower alkyl, or

R⁶ and R⁷ also together may form a bond, and

R⁵ and R⁸, together with the carbon atoms to which they are

bonded, may form an aromatic C₆-ring system,

R⁹ is hydrogen; lower alkyl; phenyl-lower alkyl optionally

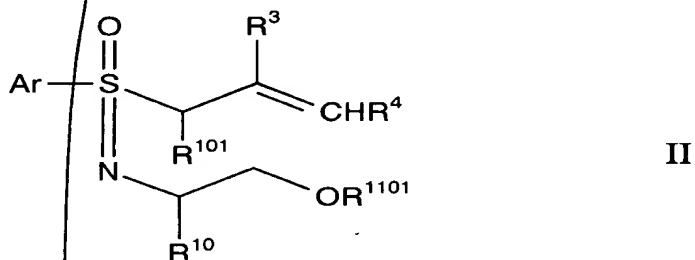
substituted one to three times in the phenyl ring by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy; or an amino protecting group, or

R⁸ and R⁹ also together may form a C₃-C₄-alkylene chain,

or an acid addition salt thereof, wherein any reactive groups which may be present in said compound of Formula Ia' may be blocked by suitable protecting groups,

said process comprising the steps of:

a) reacting a compound corresponding to formula II:



wherein

R³ and R⁴ have the above meanings,

R¹⁰¹ has the meaning given above for R¹

Ar represents phenyl optionally substituted one to three times by lower alkyl,

R¹⁰ is lower alkyl, or phenyl optionally substituted once in the phenyl ring by lower alkyl or by hydroxy protected with a suitable protecting group, or phenyl-lower alkyl optionally substituted once in the phenyl ring by lower alkyl, and

R¹¹⁰¹ stands for a silyl protecting group,

successively with

- (i) a base for the deprotonation thereof,
- (ii) an organometallic reagent corresponding to the formula VII:



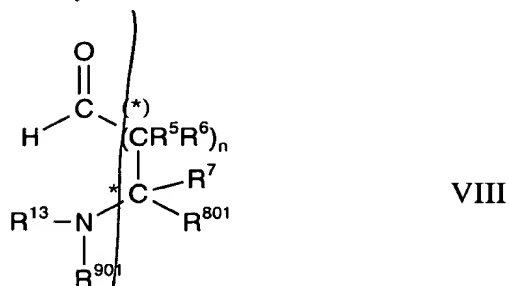
wherein

X is halogen,

M² is a tetravalent transition metal, and

R¹² is lower alkyl, phenyl or phenyl-lower alkyl, and

- (iii) a stereoisomer of a compound of the general formula VIII:



wherein

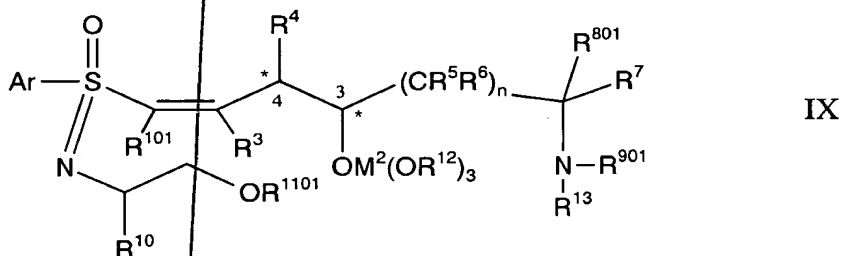
R^5, R^6, R^7 and n have the above meanings,

R^{801} has the meaning of R^8 , with any reactive groups, if necessary, being blocked by base-stable protecting groups,

R⁹⁰¹ is hydrogen or together with R⁸⁰¹ forms a C₃-C₄-alkylene chain, and

R¹³ is an amino protecting group which when cleaved leaves behind a nitrogen nucleophile,

to form a stereoisomer of a compound corresponding to the formula IX:

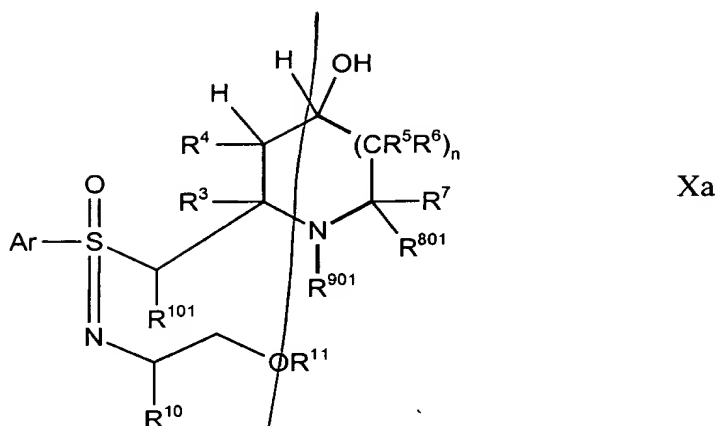


wherein

R^{101} , R^3 , R^4 , R^5 , R^6 , R^7 , R^{801} , R^{901} , R^{10} , R^{1101} , R^{12} , R^{13} , n , Ar and $M2$ have the above meanings,

and

b) converting the compound of Formula IX by treatment with a reagent for removing the group R^{13} , into a compound corresponding to formula Xa:



wherein

$R^{101}, R^3, R^4, R^5, R^6, R^7, R^{801}, R^{901}, R^{10}, n$ and Ar have the above meanings, and

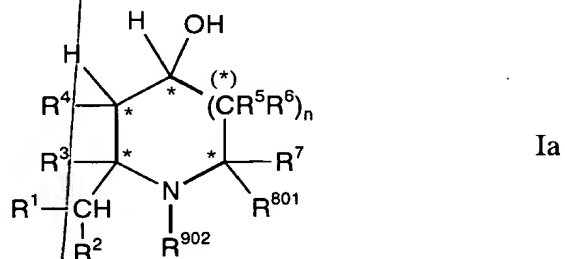
R¹¹ is hydrogen or a silyl protecting group,
and

if R⁹⁰¹ is hydrogen, blocking the nitrogen atom in the cyclic parent structure of the resulting compound of Formula Xa with a base-stable protecting group, and

cleaving off any silyl protecting group R^{11} which may still be present;

and

c) for the production of a compound corresponding to formula Ia:



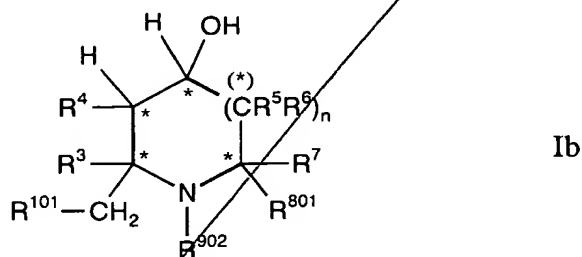
wherein

$R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{801}$ and n have the above meanings, and

R⁹⁰² stands for a base-stable protecting group or, together with R⁸⁰¹, for a C₃-C₄-alkylene chain,

reacting a compound corresponding to formula Xa or a compound produced by cleaving off the silyl protecting group R11 with a reagent

for the reductive cleavage of the sulfonimidoyl-alkyl bond, in order to obtain a compound corresponding to formula Ib:



wherein

R^{101} , R^3 , R^4 , R^5 , R^6 , R^7 , R^{801} , R^{902} and n have the above meanings,

and

optionally cleaving off any protecting groups in compounds of Formula Ia,

and

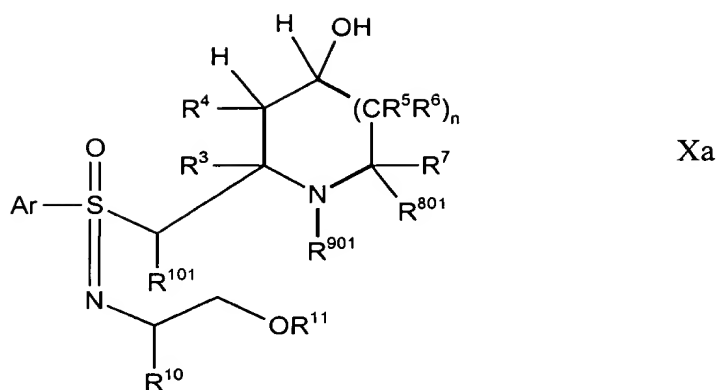
optionally reacting the optionally released NH group in the 1-position of the cyclic parent structure with a reagent capable of N-alkylation or a reagent capable of amide formation or blocking the released NH group with an amino protecting group,

thereby obtaining said compound corresponding to Formula Ia'.

23. (Amended) A process according to claim 17, wherein in step c), the sulfonimidoyl-alkyl bond in the compound corresponding to formula Xa is reductively cleaved with samarium (II) iodide.

24. (Amended) A process according to claim 17, wherein R^4 is other than hydrogen in each of the compounds corresponding to formulas Ia', Ia, Ib, II, IX and Xa.

27. (Amended) A compound corresponding to formula Xa:



wherein

n is 0 or 1,

R³ is hydrogen, and

R⁴ is hydrogen or lower alkyl or

R³ and R⁴ also together are a C₃-C₆-alkylene chain optionally containing 1 to 3 double bonds or together form the 7, 7-dimethyl [3.1.1] heptyl-system

R⁵ is hydrogen or lower alkyl, and

R⁶ is hydrogen, and

R⁷ is hydrogen,

R¹⁰ is lower alkyl, or phenyl optionally substituted once in the phenyl ring by lower alkyl or by hydroxy protected with a suitable protecting group, or phenyl-lower alkyl optionally substituted once in the phenyl ring by lower alkyl,

R¹¹ is hydrogen or a silyl protecting group,

R¹⁰¹ is hydrogen;

R⁸⁰¹ is hydrogen;

a monocyclic or bicyclic ring system selected from the group consisting of cyclopropyl, cyclopentyl, cyclohexyl, phenyl, p-tolyl and 3-indolyl;

lower alkyl; phenyl-lower alkyl or lower-alkoxy lower alkyl

or

R⁶ and R⁷ also together may form a bond, and

R⁵ and R⁸⁰¹, together with the carbon atoms to which they are bonded, may form an aromatic C₆-ring system

R⁹⁰¹ is hydrogen or together with R⁸⁰¹ forms a C₃-C₄-alkylene chain, and

Ar represents phenyl optionally substituted one to three times by lower alkyl,

wherein the sulfur-containing substituent in the 5-position and the hydroxy group in the 3-position of the cyclic parent structure are in the trans position relative to each other, and

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int wherein the substituent R⁴ in the 4-position and the hydroxy group in the 3-position of the cyclic parent structure are in the cis position relative to each other, or

a compound obtainable by removal of any protecting groups which may be present in said compound corresponding to formula Xa, or

an acid addition salt formed with a free amino group which may be present in said compound corresponding to formula Xa.

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29. (Amended) A compound according to claim 27, wherein R⁸⁰¹ and R⁹⁰¹ together form a C₃-C₄-alkylene chain.

Applicant's remarks are set forth starting on the following page.

instructions nor does it present any motivation regarding stereoselective synthesis or use of the disclosure in conjunction with other stereoselective synthesis methods. Further, the cited 3f and 3h species of Lash fall outside the scope of the amended claims.

Reggelin I teaches the synthesis of sulfoximide-substituted tetrahydrofurans. These compounds are not claimed in the present invention. Reggelin I does not teach how the sulfoximide auxiliaries could be split off from the synthesized furans, nor does the reference suggest that this might be useful. Further, Reggelin I does not suggest that the disclosed synthesis method could be extrapolated from aza pentacyclic compounds to aza hexacyclic compounds or bicyclic, tricyclic or tetracyclic ring systems of defined stereochemistry.

Reggelin II also teaches the synthesis of sulfoximide-substituted tetrahydrofurans, and discloses a method for splitting the sulfoximide auxiliary. However, the splitting method always yields a vinyl-substituted oxacyclic compound. Reggelin II does not disclose synthesis of free heterocyclic compounds without a vinyl substituent. The present invention does not claim vinyl-substituted products, instead, the present invention is directed to aza cyclic compounds with methyl substitutions.

Bolte, as discussed above, fails to present a method for synthesis of the disclosed compound. Further, while Bolte is cited for disclosing an intermediate, there is no suggestion in Bolte that the disclosed compound is an intermediate nor is there any disclosure that the compound is related to a method of stereoselective synthesis of highly substituted aza cyclic compounds.

Greene sets forth general technical background information for protective group chemistry. In view of the large number of protective groups, it is not clear how the disclosure of some or all the groups claimed would render the chosen combination obvious. Even if the protective groups of Greene can be relied upon, the previous references, whether taken singly or in combination, fail to set forth the basic formula and a method for making the same. Accordingly, the failure of the cited references to teach the present invention renders the rejection under 35 U.S.C. §103(a) improper and the rejection should be withdrawn.